The Hunter Outcome Survey (HOS)  
a Valuable Disease Registry

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Maria Paabøl Larsen is a full-time employee at Shire HGT and is responsible for the Hunter Outcome Survey
Mission of Outcomes Research
Shire HGT

To provide Quality Research Support and Leadership in and for:

- **Pre- and Post-Approval Non-Interventional Studies**
- **Collection, Reporting and Analysis**

...of real world experiences of patients and clinicians managing rare diseases.
Hunter Syndrome – MPS II

- Mucopolysaccharidosis II (MPS II)
- Glycosaminoglycans (GAGs) accumulation
- Estimate of incidence 1/162,000 for live male births
- X-linked recessive disorder which affects almost exclusively males (XY)
- Signs and symptoms affect many organ systems and can vary greatly from patient to patient
- Early visible signs include: Facial dysmorphism, hepatosplenomegaly, enlarged tongue and tonsils
- General features include: Short stature, bone dysplasia, joint stiffness and restriction, hernias, neurologic, cardiovascular, and respiratory symptoms
- Variable age of onset and variable rate of progression

The Hunter Outcome Survey (HOS)

The Hunter Outcome Survey Database was launched in 2005 and provides essential information on MPS II.

Objectives of HOS:
- Describe the population of patients affected with Hunter syndrome
- Enhance the understanding of the natural history of Hunter syndrome
- Collect long-term data on patients with Hunter syndrome
- Evaluate the impact of any therapeutic intervention on the clinical course of the disease
- Monitor the safety and effectiveness of ERT with idursulfase in a “real-world” setting
- Provide a basis for the development of clinical management guidelines for Hunter syndrome
- Fulfil post-marketing regulatory commitments
The Hunter Outcome Survey (HOS)

For patients to enrol in HOS they must:

- Have a biochemically or genetically confirmed diagnosis of Hunter syndrome
- Provide written informed consent, or have a parent or legal representative give written informed consent if the patient is less than 18 years of age.
- Not be enrolled in an ongoing blinded clinical trial.

HOS is based on collection of real-world data

- Depends on the voluntary data entry from sites

Shire HGT supports HOS by providing the necessary infrastructure, and operational as well as biostatistical support.
Key Facts on HOS (as of January 2012)

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Published Manuscripts 2005-2011

Wraith JE et al. Initial Report from HOS
Del Toro-Riera M et al. World-wide experience in the treatment of mucopolysaccharidosis type II – the Hunter Outcome Survey (HOS) registry
11 posters at ACMG, ISLSD, Congreso Brasileiro de Genetica Clinica, ESHG, IMPS, SSIEM, Spanish Society of Neurology, ASHG, COLATEL

HOS established

2005

Jones, S et al. Mortality and cause of death in mucopolysaccaridosis II (MPS II) – a historical review based on data from the Hunter Outcome Survey (HOS)
13 posters at ISLSD, ISPOR, ACMG, Brazilian Congress of Human Genetics. SSIEM, ICIEM, ASHG, SLEIMPN

Del Toro-Riera M. Follow-up of patients with Hunter syndrome: the Hunter Outcome Survey (HOS) registry
4 posters at SSIEM, ASHG, IWLSI, COLATEL

2007

Muenzer et al. Idursulfase treatment of Hunter syndrome in children younger than 6 years: Results from the Hunter Outcome Survey
Kampmann et al. Prevalence and Characterization of Cardiac Involvement in Hunter Syndrome
Keilmann et al. Hearing Loss in Patients with MPSII
Burton et al. Incidence and timing of infusion-related reactions in patients with mucopolysaccharidosis type II (Hunter syndrome) on idursulfase therapy in the real-world setting: a perspective from the Hunter Outcome Survey (HOS)

2008

Burton BK et al. Infusions at home: data from HOS – the Hunter Outcome Survey – on patients receiving therapy with idursulfase

2009

Link B et al. Orthopedic manifestations in patients with mucopolysaccharidosis type II (Hunter syndrome) enrolled in the Hunter Outcome Survey
C Alcalde Martin et al. First experience of enzyme replacement therapy with idursulfase in Spanish patients with Hunter syndrome under 5 years of age: Case observations from the Hunter Outcome Survey (HOS)
NJ Mendelsohn et al. Importance of surgical history in diagnosing mucopolysaccharidosis type II (Hunter syndrome): data from the Hunter Outcome Survey (HOS)

2010

16 posters LDN, COLATEL, ACMG, German ENT Society, European Society of Pediatric Otohinolaryngology (ESPO), IMPS SSIEM, 3rd Congress of European Academy of Paediatrics (EAP), Congreso Argentino de Neurologia Infantil, IWLSI

2011

Keilmann et al. Hearing Loss in Patients with MPSII
Key findings on Hunter Syndrome from HOS publications

- By six years of age approximately 50% of patients show cardiovascular abnormalities, which was shown to increase to 90% of patients by 15 years of age.
- Cardiovascular manifestations included valve disease (57% of patients), murmur (53%), and cardiomyopathy (8%).
- Analysis of data for 216 patients with Hunter syndrome found the most common clinical symptoms prior to diagnosis were:
  - Characteristic facial features (96%) – observed at a median age of 2.8 years.
  - Enlarged spleen/liver (87%) – observed at a median age of 3.5 years.
  - Hernia (75%) – observed at a median age of 1.8 years.
  - Otitis (70%) – observed at a median age of 1.7 years.
  - Enlarged tonsils adenoids (67%) – observed at a median age of 3.4 years.

Limitations of Registries

In general, all registries suffer from threats to validity, bias, and confounding.

- Data are generally not 100% source data verified
- Variability in data definitions, interpretation, abstraction and collection intervals
- Inability to perform desired analyses due to limitations of data captured
- Data are collected without a predetermined sample size, which could result in a lack of statistical power for some inferential analyses.
- Analysis of observational data requires experienced biometrics personnel
- Perceived diminished value of research evidence than controlled trials. Journal reviewers may be less accepting of observational data
- Data entry depends on the time, resources, and engagement of the participating sites.
Quality & Completeness of Data

- Quality and completeness of data are dependent on the diligent work of the sites.

- High quality of data is crucial for:
  - Capturing patient safety issue
  - Ensuring strong evidence for publications and treatment guidelines
  - Capturing data trends
  - Obtaining the full potential of data collected

- Core Data Variables have been defined.
How to Improve Overall Completeness

- All HOS investigators receive training in HOS procedures and processes.
- Regular monitoring activities take place.
- Shire Data manager ensures querying of data and follow up.
- Important to support and encourage sites to prioritize data entry.
- Operational conduct is adapted to the country and site specific conditions to ensure the right support is given.
- Sites may periodically be audited by a representative of Shire HGT, which may reduce the likelihood of inconsistent data entry.
Summary

- HOS has proven to be invaluable in providing real-world data on Hunter syndrome over the past 6 years: more than 12 publications
- Long-term clinical outcomes and safety of treatment need to be assessed using real-world data
- HOS Boards and Working groups help focus the questions and data analyses in HOS
- Collaboration with patient organizations and health authorities is necessary and valuable
- Important to also have consistent funding and full-time qualified staff continuously overseeing the operational conduct of the registry
- Through ongoing collaboration between participating expert physicians, HOS will help continue to expand the evidence base of knowledge around Hunter syndrome and its management
- …More unanswered questions to be answered in the future
Acknowledgement

Thanks to all patients, physicians and clinical staff for efforts and contribution to HOS